



## SEQUENCE LISTING

<110> Genzyme Corporation  
Wadsworth, Samuel  
Armentano, Donna  
Gregory, Richard J.  
Parsons, Geoffrey

<120> Methods of Treating Diabetes and Other Blood Sugar Disorders

<130> 5062CIP

<140> US 10/716,326

<141> 2003-11-17

<150> US 10/215,272

<151> 2002-08-07

<150> US 60/310,982

<151> 2001-08-08

<160> 54

<170> PatentIn version 3.2

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<212> DNA

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<223> Nucleotide sequence of SEAP.GLP-1Gly8

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tgggccacgg cgagggcacc ttcaccagcg acgtgagcag ctacctggag ggccaggccc 120

ccaaggagtt catcgcttgg ctggtgaagg gccgcggc 158

<210> 2

<211> 48

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<213> Artificial Sequence

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<223> Amino acid sequence of SEAP.GLP-Gly8

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Gly His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
20 25 30

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
35 40 45

<210> 3

<211> 250

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<223> Nucleotide sequence of Exendin-4.GLP-1Gly8

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ccagctccga gagcttcgcc aagcgcacga agcggcacgg cgagggcacc ttcaccagcg 180  
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<210> 4  
<211> 78  
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<220>  
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<400> 4

Met Lys Ile Ile Leu Trp Leu Cys Val Phe Gly Leu Phe Leu Ala Thr  
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Leu Phe Pro Ile Ser Trp Gln Met Pro Val Glu Ser Gly Leu Ser Ser  
20 25 30

Glu Asp Ser Ala Ser Ser Glu Ser Phe Ala Lys Arg Ile Lys Arg His  
35 40 45

Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln  
50 55 60

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
65 70 75

<210> 5  
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<223> Nucleotide sequence of Helodermin.GLP-1Gly8

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agacagacca gagactgaag cgcacaaagc gccacggcga gggcaccttc accagcgacg 180  
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245

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20 25 30

Glu Asp Ser Glu Thr Asp Gln Arg Leu Lys Arg Ile Lys Arg His Gly  
35 40 45

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala  
50 55 60

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
65 70 75

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tgggcagcca tgccaagggtg agctccccac agaagcgcat caagcgccac ggcgagggca 180  
ccttcaccag cgacgtgagc agctacctgg agggccaggc cgccaaggag ttcacgcct 240  
ggctggtgaa gggccgcggc 260

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<223> Amino acid sequence of GIP.GLP-1Gly8

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Met Val Ala Thr Lys Thr Phe Ala Leu Leu Leu Ser Leu Phe Leu  
1 5 10 15

Ala Val Gly Leu Gly Glu Lys Lys Glu Gly His Phe Ser Ala Leu Pro  
Page 3

20

25

30

Ser Leu Pro Val Gly Ser His Ala Lys Val Ser Ser Pro Gln Lys Arg  
 35 40 45

Ile Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr  
 50 55 60

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly  
 65 70 75 80

Arg Gly

<210> 9

<211> 266

<212> DNA

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<223> Nucleotide sequence of IGF-1 (furin).GLP-1Gly8

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ccctgtgcct gctgaccttc accagctccg ccacagccaa gcgcatacaag cgccacggcg 180

agggcacctt caccagcgac gtgagcagct acctggaggg ccaggccgcc aaggagtcca 240

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<211> 84

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<223> Amino sequence of IGF-1 (furin).GLP-1Gly8

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Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu  
 20 25 30

Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala  
 35 40 45

Lys Arg Ile Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser  
 50 55 60

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val  
65 70 75 80

Lys Gly Arg Gly

<210> 11  
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<223> Nucleotide sequence of IGF-1.GLP-1Gly8

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ccctgtgcct gctgaccttc accagctccg ccacagccca cggcgagggc accttcacca 180  
gcgacgtgag cagctacctg gagggccagg ccgccaagga gttcatcgcc tggctggtga 240  
agggccgcgg c 251

<210> 12  
<211> 79  
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<223> Amino acid sequence of IGF-1.GLP-1Gly8

<400> 12  
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Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu  
20 25 30  
Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala  
35 40 45  
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
50 55 60  
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
65 70 75

<210> 13  
<211> 167  
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<223> Nucleotide sequence of Preproglucagon.GLP-1Gly8

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aaggcagctg gcaacacggc gagggcacct tcaccagcga cgtgagcagc tacctggagg 120  
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<210> 14  
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Gly Ser Trp Gln His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser  
20 25 30

Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys  
35 40 45

Gly Arg Gly  
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<210> 15  
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<223> Nucleotide sequence of Alpha-1 antitrypsin.GLP-1Gly8

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gctgcctggt ccctgtctcc ctggctcacg gcgagggcac cttcaccagc gacgtgagca 120  
gctacctgga gggccaggcc gcccaaggagt tcatcgctg gctggtgaag ggccgcggc 179

<210> 16  
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<223> Amino acid sequence of Alpha-1 antitrypsin.GLP-1Gly8

<400> 16  
Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys  
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Cys Leu Val Pro Val Ser Leu Ala His Gly Glu Gly Thr Phe Thr Ser  
 20 25 30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala  
 35 40 45

Trp Leu Val Lys Gly Arg Gly  
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<210> 17  
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 atgccaacaa gattctgaac agaccaaga ggcatgggga gggcaccttc accagcgacg 180  
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<210> 18  
 <211> 77  
 <212> PRT  
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<220>  
 <223> Amino acid sequence of Factor IX.GLP-1Gly8

<400> 18

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr  
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Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu  
 20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg His Gly  
 35 40 45

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala  
 50 55 60

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
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<210> 19  
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<223> Nucleotide sequence of Exendin-4 (IGF-1).GLP-1Gly8

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ccagctccga gagccctctg aagcctgcca agtctgccag acatggagag ggcaccttca      180
catctgacgt gaggcagctac ctggagggcc aggccgccaa ggagttcatc gcctggctgg      240
tgaagggccg cggc                                          254
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<223> Amino acid sequence of Exendin-4 (IGF-1).GLP-1Gly8

<400> 20

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Leu Phe Pro Ile Ser Trp Gln Met Pro Val Glu Ser Gly Leu Ser Ser
      20              25              30

Glu Asp Ser Ala Ser Ser Glu Ser Pro Leu Lys Pro Ala Lys Ser Ala
      35              40              45

Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
      50              55              60

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
65              70              75              80
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<210> 21

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<223> GLP-1(7-37)

<400> 21

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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
      20              25              30
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<210> 22  
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<220>  
<223> Modified GLP-1 molecule; Gly8-GLP-1 (7-37)

<400> 22

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1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
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<210> 23  
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<220>  
<223> Modified GLP-1 molecule; GLP-1 (7-34)

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His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys  
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<210> 24  
<211> 29  
<212> PRT  
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<220>  
<223> Modified GLP-1 molecule; GLP-1 (7-35)

<400> 24

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly  
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<210> 25  
<211> 30  
<212> PRT  
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<220>  
<223> Modified GLP-1 molecule; GLP-1 (7-36)

<400> 25

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
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1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg  
20 25 30

<210> 26  
<211> 31  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Modified GLP-1 molecule; Val8-GLP-1 (7-37)

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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
20 25 30

<210> 27  
<211> 31  
<212> PRT  
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<220>  
<223> Modified GLP-1 molecule; Gln9-GLP-1 (7-37)

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His Ala Gln Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
20 25 30

<210> 28  
<211> 31  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Modified GLP-1 molecule; Thr16-Lys18-GLP-1 (7-37)

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His Ala Glu Gly Thr Phe Thr Ser Asp Thr Ser Lys Tyr Leu Glu Gly  
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
20 25 30

<210> 29  
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<212> PRT  
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<220>

<223> Modified GLP-1 molecule; Lys18-GLP-1 (7-37)

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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
20 25 30

<210> 30

<211> 31

<212> PRT

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<220>

<223> Modified GLP-1 molecule; D-Gln9-GLP-1 (7-37)

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1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Gln Trp Leu Val Lys Gly Arg Gly  
20 25 30

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<211> 36

<212> PRT

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<223> Modified GLP-1 molecule; GLP-1 (2-37)

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Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val  
20 25 30

Lys Gly Arg Gly  
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<210> 32

<211> 35

<212> PRT

<213> Artificial Sequence

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<223> Modified GLP-1 molecule; GLP-1 (3-37)

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Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys

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Gly Arg Gly

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<210> 33

<211> 32

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<223> Modified GLP-1 molecule; GLP-1 (6-37)

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Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu

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Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly

                  20                    25                    30

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<221> misc\_feature

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<223> Xaa can be any naturally occurring amino acid

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<210> 35

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<221> misc\_feature

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<223> Xaa can be any naturally occurring amino acid

<400> 35

Arg Xaa Arg Arg

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<210> 36

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<223> Recognition site for furin cleavage

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<222> (1)..(1)

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<222> (3)..(3)

<223> Xaa can be any naturally occurring amino acid

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<222> (4)..(4)

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<400> 36

Xaa Arg Xaa Xaa Arg

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<210> 37

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<223> Xaa can be any naturally occurring amino acid

<400> 37

Arg Xaa Xaa Arg

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<400> 38

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Pro Leu Lys Pro Ala Arg Ser Ala Arg  
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<210> 42  
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<210> 43  
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<400> 43

Pro Leu Ala Pro Ala Lys Ser Ala Arg  
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<210> 44

<211> 9

<212> PRT

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<223> Modified IGF-signal 1 sequence

<400> 44

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<210> 45

<211> 9

<212> PRT

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<400> 45

Pro Leu Arg Pro Ala Lys Ser Lys Arg  
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<210> 46

<211> 9

<212> PRT

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<220>

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<400> 46

Pro Leu Arg Pro Ala Arg Ser Lys Arg  
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<210> 47

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Modified IGF-1 signal sequence

<400> 47

Pro Leu Ala Pro Ala Lys Ser Lys Arg  
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<210> 48

<211> 9  
<212> PRT  
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<400> 48

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<210> 49  
<211> 9  
<212> PRT  
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<400> 49

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<210> 50  
<211> 9  
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<223> Modified IGF-1 signal sequence

<400> 50

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<210> 51  
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<220>  
<223> 5705DA

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<210> 52  
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<220>  
<223> 5706DA

<400> 52  
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<210> 53  
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 <212> DNA  
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 <223> Annealed oligonucleotides containing a polylinker for cloning  
  
 <400> 53  
 gatctcctag gggtttcgaa accactagta agcttaccgc atgccttaag g 51  
  
 <210> 54  
 <211> 51  
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